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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,138	07/21/2006	Alexei Kharitonenkov	X-16455	1688

25885 7590 01/12/2009

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EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
01/12/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/587,138	KHARITONENKOV ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response of 06 October 2008 has been received and entered. Claims 1-8 are currently pending and under examination in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Glasebrook et al. (WO 03/011213) in combination with Hauner (Diabetes Metab. Res. Rev. 18: S10-S15, 2002) for the reasons of record in the previous Office action.

Glasebrook et al. teach a method of treating a mammal exhibiting one or more of Type 2 diabetes, obesity, insulin resistance, hyperinsulinemia, glucose intolerance, or hyperglycemia by administration of FGF-21 (see page 4). Glasebrook et al. also teach that there are a number of pharmacological approaches for the treatment of Type 2 diabetes available, which have different modes of action, including thiazol-idinediones which enhance insulin action and promote glucose utilization and inhibit hepatic glucose

output. Glasebrook et al. also state that the pharmacological approaches for treating Type 2 diabetes can be utilized individually or in combination therapy and that each approach has its limitations and adverse side effects (see page 2). Glasebrook et al. teaches that FGF-21 increases glucose uptake, and that uptake is further increased in the presence of insulin (see Figures 3 and 4).

Hauner teaches that thiazolidinediones (TZDs) are a class of antidiabetic drugs that improve metabolic control in patients with type 2 diabetes via improving insulin sensitivity which is accomplished by activation of the gamma isoform of the peroxisome proliferator-activated receptor (see abstract). Hauner also teaches that type 2 diabetes is a component of metabolic syndrome (see paragraph 1). Hauner also teaches that rosiglitazone and pioglitazone are TZDs that have been approved for the treatment of diabetes (page S11, column 1, paragraph 2). Hauner also teaches that the antidiabetic effect of TZDs is derived via sensitization of target tissues to the action of insulin (page S11, column 2, paragraph 3).

It would have been prima facie obvious at the time of the instant invention to combine the teachings of Glasebrook et al. and Hauner and treat type 2 diabetes and/or metabolic syndrome with the combination of FGF-21 and a TZD (such as rosiglitazone and pioglitazone) in order to improve insulin sensitivity and glucose uptake in the individual being treated. It is well known in the art to combine different treatment methods, and this is acknowledged in Glasebrook et al. Many times the use of combined therapies permits lower dosages of the individual drugs, which reduces any adverse side effects of the drugs. Furthermore, one would be motivated to use the

combination of FGF-21 and TZDs for the treatment of type 2 diabetes (or metabolic syndrome) because TZDs increase insulin sensitivity and FGF-21 has a greater effect on glucose uptake in the presence of insulin. Because the two drugs act via different mechanisms, it is not unexpected that the combination might produce a better effect than either drug alone or as a simple addition of their effects. It is noted that the instant specification asserts that the effects of the two drugs together is synergistic, but again, this does not appear to be an unexpected result since the two drugs act via different mechanisms and because TZDs appear to enhance a response that is known to enhance the response of FGF-21 (namely glucose uptake in the presence of insulin wherein TZDs increase insulin sensitivity). Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made, absent evidence to the contrary.

Applicant argues at page 4 of the response that FGF-21 stimulates glucose uptake in the absence of insulin and therefore, the obviousness rejection has been rebutted. Applicant's argument has been fully considered, but is not persuasive. As pointed out in the previous Office action, Glasebrook et al. teaches that FGF-21 increases glucose uptake (in the absence of insulin - Figure 3), and that uptake is further increased in the presence of insulin (see Figure 4). Therefore, Glasebrook et al. was not misinterpreted and did not need clarification.

Applicant argues at page 5 of the response that rosiglitazone alone has no effect on glucose uptake in 3T3 cells, but that the combination of rosiglitazone and FGF-21 resulted in a synergistic effect that was almost 3 times the effect of FGF-21 alone on glucose uptake. Applicant asserts that a person of skill in the art would not predict or

expect such a result and therefore, such an effect cannot be obvious. Applicant's argument has been fully considered, but is not found persuasive. First, the claims are directed to a method of treating a mammal having type 2 diabetes or metabolic syndrome by the administration of FGF-21 in combination with thiazolidinedione sufficient to achieve reduction in tryglycerides, decrease in insulin resistance, reduction of hyperinsulinemia, increase in glucose tolerance, or reduction of hyperglycemia. Because thiazolidinediones (TZDs) are a class of antidiabetic drugs that improve metabolic control in patients with type 2 diabetes via improving insulin sensitivity, the lack of an effect on glucose uptake in 3T3 cells in the absence of insulin is not surprising. Glasebrook et al. clearly teach the administration of FGF-21for the treatment of type 2 diabetes as well as teaching that combination therapy is common including use of thiazol-idinediones which enhance insulin action and promote glucose utilization and inhibit hepatic glucose output. Glasebrook et al. also state that the pharmacological approaches for treating Type 2 diabetes can be utilized individually or in combination therapy and that each approach has its limitations and adverse side effects (see page 2). Glasebrook et al. teach that FGF-21 stimulates glucose uptake in an insulin independent manner and is further increased in the presence of insulin (see Figures 3 and 4). Therefore, the combination of FGF-21 and thiazolidinediones for the treatment of type II diabetes was clearly suggested in the art prior to the claimed invention.

With regard to the alleged unexpected results, Hauner teaches that thiazolidinediones (TZDs) are a class of antidiabetic drugs that improve metabolic control in patients with type 2 diabetes via improving insulin sensitivity which is

accomplished by activation of the gamma isoform of the peroxisome proliferator-activated receptor (see abstract). Hauner also teaches that type 2 diabetes is a component of metabolic syndrome (see paragraph 1). Hauner also teaches that rosiglitazone and pioglitazone are TZDs that have been approved for the treatment of diabetes (page S11, column 1, paragraph 2). Hauner also teaches that the antidiabetic effect of TZDs is derived via sensitization of target tissues to the action of insulin (page S11, column 2, paragraph 3). The claims are directed to a method of treatment of a mammal, therefore, the mammal would have endogenous insulin. Applicant's arguments directed to experiments in the absence of insulin are noted, but are not applicable to the instant claims. One of ordinary skill in the art would have use the combination of FGF-21 and thiazolidinediones for the treatment of type II diabetes and because the two drugs act via different mechanisms, it is not unexpected that the combination might produce a better effect than either drug alone or as a simple addition of their effects. Therefore, the invention as a whole would have been *prima facie* obvious at the time it was made, absent evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1647